UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,084	05/24/2000	Keiya Ozawa	50026/012002	5150

21559 7590 08/23/2006

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/577,084	OZAWA ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,10,14,15,18,20 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10,14,15,18,20 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/05;11/23/05;3/22/06;7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 6/2/06 has been entered in full. Claims 1, 10 and 22-24 are amended. Claims 9, 16, 17, 19 and 21 are canceled. New claims 25 and 26 are added.

Claims 1, 4-8, 10, 14, 15, 17, 18 and 20-26 are under consideration in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The Information Disclosure Statements of 9/2/05; 11/23/05; 3/22/06; and 7/31/06 have each been considered.

Priority

As set forth in the 11/29/05 Office Action (pg 2) there is no written support for the currently claimed invention in the parent application 09/142,305. The '305 application does not mention fusion proteins comprising c-mpl. Therefore, the current application merits priority as of its filing date, 5/24/2000. Applicants in the 6/2/06 response do not provide any arguments to the contrary.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (11/29/05).

All rejections of claims 16, 17 and 21 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 10, 14, 15, 18, 20 and 24 under 35 U.S.C. § 112, first paragraph at pg 3-4 for containing new matter is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 10, 14, 15, 18, 20 and 24 under 35 U.S.C § 112, second paragraph, at pg 4 for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 1, 4, 6-8, 20 and 23 under 35 U.S.C. § 103(a) at pg 5-8 as being unpatentable over Gurney et al (1995) in view of Jackson et al is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 1, 4-8, 10, 14, 15, 18, 20 and 22-24 under 35 U.S.C. § 103(a) at pg 8-9 as being unpatentable over Ito et al (1997) in view of Gurney et al (1995) is *withdrawn* in view of Applicants' amendments to the claims, Applicants' arguments with regard to claim 1 at pg 9-10 of the 6/2/06 response, and further consideration by the Examiner. Please note the new rejection of claim 10 and dependent claims 14, 15, 18, 20 and 24 set forth below.

The provisional double patenting rejection of claims 1, 4 and 23 over claims 1, 3 and 4 of copending Application No. 09/142305 in view of Solar et al (1998) is *withdrawn* in view of Applicants' amendments to the claims.

The provisional double patenting rejection of claims 6-8, 10, 14, 17, 18, 20 and 24 over claims 1, 3 and 4 of copending Application No. 09/905592 in view of Solar et al (1998) is *withdrawn* in view of Applicants' amendments to the claims and on further consideration by the Examiner.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 1, 4-8, 20, 22, 23, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 1 was amended 6/2/06 to include the limitation that the "second polypeptide comprises the extracellular region of a granulocyte colony stimulating factor receptor and the cytoplasmic region of c-mpl". It is recognized by the Examiner that this amendment incorporates a limitation that was previously present in dependent claim 22 (Claim 22 was previously submitted as a new claim on 5/4/2004). However, on further consideration of the specification, claim 1 is considered to encompass new matter.

In making the amendment to claim 1, Applicants' response (pg 6) points to support in the specification at page 31, lines 19-24. However, this portion of the specification refers to the "[t]he extracellular region of ΔGCR and the cytoplasmic domain of c-mpl". Therefore, while the instant claim refers to the "the extracellular region" of granulocyte colony stimulating factor receptor (also known as G-CSFR or GCR), the specification refers to the "the extracellular region of ΔGCR". These two phrases differ in scope. The extracellular region of G-CSFR encompasses the extracellular region of the full-length receptor, while the ΔGCR molecule "is deficient in the 5th residue, Glu, through the 195th residue, Leu, of the G-CSF receptor extracellular domain" (see pg 14, lines 3-4). Furthermore, the specification only teaches working examples comprising ΔGCR and c-mpl (for example, Figure 20). The Examiner cannot find any teaching in the specification describing a receptor comprising the full-length G-CSFR extracellular domain and the cytoplasmic domain of c-mpl. Therefore, there is no conception of this specific genus of molecules in the specification, nor does the concept of the specific genus flow naturally from the disclosure. As such, the specification as originally filed lacks support for the genus of molecules encompassed by the amended claims. Claims 4-8, 20, 23, 25 and 26 depend from claim 1 and therefore encompass new matter for the same reason. Claim 22 depends from claim 10 but includes a further limitations of similar nature to claim 1; that is, claim 22 limits the claimed vector to encoding a second polypeptide comprising the extracellular region of granulocyte colony stimulating factor receptor and c-mpl.

New claim 25 also contains new matter for the following reason. The claim is directed to a kit of claim 20 "wherein said kit further comprises a vector comprising an exogenous gene." Claim 20 encompasses a kit comprising a vector of claim 7 or claim 10 and a ligand. Therefore claim 25 is directed to a kit comprising two vectors (the vector of claim 7 or claim 10 and another vector comprising an exogenous gene) and a ligand. The Examiner cannot find any teachings in the specification describing a kit with two vectors and a ligand. Applicants' 6/2/06 response (pg 6) points to support for new claim 25 in the specification at pg 5, lines 21-25, pg 6, lines 24-26 and pg 8, lines 2-7. However, the Examiner can find no teachings regarding kits on the referenced pages

and lines. Therefore the specification as originally filed lacks support for the genus of kits encompassed by the new claim. It is noted that the specification provided by Applicants on 5/24/2000 does not contain any line numbers on the pages. Therefore, if Applicants maintain that the referenced pages of the specification do provide support for the claimed kit, Applicants are requested to quote the exact text that provides such support.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 1, 4-8, 10, 14, 15, 18, 20 and 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what is modified by the phrase "or a proliferation inducing part thereof". It is unclear whether "or a proliferation inducing part thereof" modifies "the cytoplasmic domain of c-mpl", "the extracellular region of a granulocyte colony stimulating factor receptor", or both.

Claim 10 is indefinite because it recites "a c-mpl" and the metes and bounds of this phrase are unclear. In this regard, the claim would be rendered definite if amended to delete the word "a" such that the claim only recites "c-mpl".

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

Claims 10, 14, 15, 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al, 1997 (Blood. 90(10): 3884-3892; cited previously) in view of Drachman et al (1997. Proc Natl Acad Sci USA. 94: 2350-2355).

Ito teaches a fusion protein comprising the granulocyte colony stimulating factor receptor (G-CSFR) and the estrogen receptor hormone-binding domain (ER-HBD) (Fig 1a and pg 3886) that is functional in proliferation of the murine pro-B cell line Ba/F3 (Fig 3). Ito teaches DNA, vectors and isolated cells encoding the fusion protein (pg 3885). Ito teaches a mutant ER protein that binds synthetic 4-hydroxytamoxifen but not estrogen and teaches the advantage of using this mutant ER in the fusion protein of the invention

(pg 3891). Ito further teaches co-transfection with a plasmid comprising the exogenous blasticidin gene. Therefore, Ito teaches all of the limitations of the claims, except that (1) the vector encodes a fusion protein comprising c-mpl and (2) the exogenous gene and the DNA encoding the fusion protein are present on the same molecule (i.e., a single vector rather than two discrete vectors). Ito further teaches that "[t]he strategy used in this study is based on the finding that estrogen can activate fusion proteins between ER-HBD and a wide variety of heterologous proteins" (pg 3888) and "[v]arious modifications are possible to improve the system as described here. We are also constructing similar chimeric genes using other growth factor receptor genes such as *c-kit* and erythropoietin receptor" (pg 3891).

Drachman teaches a vector encoding full-length c-mpl and also comprising an exogenous neomycin resistance gene (See "Receptor Constructs, pg 2351). Drachman teaches that this vector encodes a c-mpl protein that supports proliferation of Ba/F3 cells in response to thrombopoietin (Fig 2). Drachman further teaches that "[l]ike the receptors for growth hormone, erythropoietin and granulocyte colony-stimulating factor, Mpl is believed to be activated through homodimerization..." (pg 2350).

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute c-mpl as taught by Drachman for G-CSFR in the vector taught by Ito, and to further include an exogenous gene encoding neomycin resistance as taught by Drachman. The person of ordinary skill in the art would be motivated to do so in order to use the vector to selectively amplify Ba/F3 hematopoietic cells, and because Ito suggests modifications using other growth factor receptor genes such as the erythropoietin receptor. The person of ordinary skill in the art would have had a reasonable expectation of success because Ito teaches all of the techniques necessary to make a vector encoding fusion protein between a receptor and ER-HBD, and to use it for proliferation of Ba/F3 hematopoietic cells, and in the absence of other evidence, c-mpl would work as well as G-CSFR in the fusion protein encoded by the vector.

Applicants' arguments (6/2/06; pg 10-14) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 6/2/06, Applicants argue that amended claim 10 is non-obvious over the cited art because it incorporates the limitations of canceled claim 16, which was not rejected in the previous Office Action (11/29/05). Applicants further argue that Gurney fails to teach a vector containing both an exogenous gene and a DNA encoding the claimed fusion protein. Applicants argue that in view of the disparity in the structures, ligand binding mechanisms and signal transduction mechanisms of growth hormone receptors and steroid hormone receptors, Gurney also fails to teach or suggest the desirability of combining a ligand-binding domain of a steroid receptor with c-mpl. Applicants argue that Ito does not teach c-mpl, or provide any motivation to combine its teachings with those of Gurney. Applicants argue that Ito mentions other possible growth factor chimeras (e.g., *c-kit* or erythropoietin receptor) but teaches away from the desirability of using receptors other than G-CSFR. In support of this argument, Applicants cite teachings of Ito on page 3891 that G-CSFR derived molecules may be safer than those of other receptor for clinical use.

Applicants' arguments have been fully considered but are not found persuasive. On further consideration of the relevant literature, the Examiner considers that amended claim 10 is obvious over Ito in view of Drachman for the reasons set forth above. It is true that Ito teaches that G-CSFR-derived molecules may be safer for clinical application that molecules derived from other receptors. However, Ito teaches other uses for the chimeric receptors than clinical in vivo application. Specifically, Ito teaches that the chimeric receptors can be used for ex vivo amplification of cells; for example see page 3884, "selection and enrichment of transduced hematopoietic stem cells ex vivo may be a feasible approach" and page 3890, "[i]n addition, this modified amplifier gene will be applicable to the ex vivo expansion of transduced hematopoietic stem/progenitor cells".

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al, 1997 (Blood. 90(10): 3884-3892; cited previously) in view of Drachman et al (1997. Proc Natl Acad Sci USA. 94: 2350-2355) as applied to claim 10 above, and further in view of

Picard, 1999 (Picard, Ch 11 (pg 261-274) in Nuclear Receptors: a Practical Approach (D. Picard, ed) Oxford University Press, Oxford, 1999).

The teachings of Ito and Drachman as applied to claim 10 are described above. Neither Ito nor Drachman teaches steroid receptor hormone binding domains from androgen, progesterone, glucocorticoid or mineral corticoid receptor.

Picard teaches "Regulation of heterologous proteins by fusion to a hormone binding domain" (see title, pg 261). Picard further teaches fusions using the hormone-binding domain (HBD) of either the estrogen, androgen, progesterone, glucocorticoid or mineral corticoid receptor (Table 1). Picard teaches that each of these steroid receptors forms a stable complex on ligand binding (pg 268).

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute c-mpl as taught by Drachman for G-CSFR in the vector taught by Ito, and to further include an exogenous gene encoding neomycin resistance as taught by Drachman, and to further substitute any of the steroid hormone receptor ligand binding domains taught by Picard. The person of ordinary skill in the art would be motivated to do so in order to use the vector to selectively amplify Ba/F3 hematopoietic cells, and because Ito suggests modifications using other growth factor receptor genes such as the erythropoietin receptor, and because Picard teaches the interchangeability of steroid hormone receptor ligand binding domains in heterologous fusion proteins. The person of ordinary skill in the art would have had a reasonable expectation of success because Ito teaches all of the techniques necessary to make a vector encoding fusion protein between a receptor and ER-HBD, and to use it for proliferation of Ba/F3 hematopoietic cells, and in the absence of other evidence, c-mpl would work as well as G-CSFR, and the androgen, progesterone, glucocorticoid or mineral corticoid receptor would work as well as the estrogen receptor, in the fusion protein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10, 14, 15, 18, 20 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8, 12, 15, 17 and 22 of copending Application No. 09/905592 in view of Ito et al, 1997 (Blood. 90(10): 3884-3892; cited previously) and further in view of Drachman et al (1997. Proc Natl Acad Sci USA. 94: 2350-2355). It is noted that the claims of the '592 application were last amended 11/7/05. An amendment after final was filed 6/29/06 with amended claims; however, the amended claims were not entered into the record (see the Advisory Action mailed 7/20/06).

The '592 application is a divisional application of copending Application No. 09/142305. As noted above in the section titled "Priority", the instant application is a CIP of 09/142305 and claims priority to the filing date of 09/142305. However, the disclosure of 09/142305 does not disclose the fusion proteins comprising c-mpl. Therefore, with regard to the species of c-mpl, the instant application does not merit priority to the disclosure of 09/142305.

Claims 8, 12, 15, 17 and 22 of '592 contain all of the limitations of claims 10, 14, 15, 18 and 20 of the instant application, except that the vector is limited to one encoding

the G-CSF receptor in the '592 application, and is limited to one encoding c-mpl in the instant application.

The teaching of Ito and Drachman are described above in the section entitled "Claim Rejections - 35 USC § 103".

It would be obvious to the person of ordinary skill in the art at the time the invention was made to substitute c-mpl as taught by Drachman for G-CSFR in the vector encoding the fusion protein taught by the '592 application. The person of ordinary skill in the art would be motivated to do so in order to use the vector to selectively amplify Ba/F3 hematopoietic cells, and because Ito suggests modifications using other growth factor receptor genes such as the erythropoietin receptor. The person of ordinary skill in the art would have had a reasonable expectation of success because the '592 application teaches all of the techniques necessary to make a vector encoding fusion protein between a receptor and ER-HBD, and to use it for proliferation of Ba/F3 hematopoietic cells, and in the absence of other evidence, c-mpl would work as well as G-CSFR in the fusion protein encoded by the vector.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600